AstraZeneca

Date: December 7, 2004

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2004D-0378
Response to FDA Call for Comments
International Conference on Harmonisation; Draft Guidance on S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

Dear Sir or Madam:

Reference is made to the September 13, 2004 Federal Register notice announcing the request for comments on International Conference on Harmonisation; Draft Guidance on S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Bonnie Clemmer, Project Coordinator, at 302-885-1942.

Sincerely,

Bonnie L. Clemmer for Lewis B. Kinter

Lewis B. Kinter, Ph.D.
Safety Assessment US
Telephone: 302-885-8193
Fax: 302-885-1742

LBK\blc

Enclosure

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Comments from AstraZeneca on International Conference on Harmonisation Draft Guidance on S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

(Docket Number: 2004D-0378)

General Comments:

The original objective of the ICHS7B process, as stated in the ICHS7A, was to "*present some currently available methods and discuss their advantages and disadvantages*". The document has developed into a formal draft guideline that goes well beyond this objective.

There are inconsistencies (e.g., Objectives, Timing) between the draft ICHS7B and other guidelines referring to non-clinical safety evaluation (e.g., ICHS7A, M3). Therefore the implementation of the ICHS7B document, in its current form, would provide confusion, as opposed to clarity, to both sponsors and regulatory agencies. Based on current (ICHS7A) and emerging (E14) guidelines, it is unlikely that that these inconsistencies can be resolved in a satisfactory way.

Considering that the ICHS7B is aimed at addressing a subcomponent of the ICHS7A "core battery" and "follow-up" studies (drug effects on cardiac repolarization as part of the global assessment of cardiovascular function), then a way forward could be to amend the ICHS7A appropriately. Minor amendments could be inserted into the ICHS7A to reflect the latest scientific thoughts wherever appropriate (e.g., cardiovascular & respiratory sections).

Consequently, we recommend that the ICHS7B process should be discontinued and the ICHS7A amended as detailed below. Alternatively, ICHS7B could be revised (to remove inconsistencies with ICH S7A) and positioned as an Appendix to the ICHS7A focusing on its original objective (i.e., to "*present some currently available methods and discuss their advantages and disadvantages*").

Suggested amendments to ICH S7A - link attached
http://www.emea.eu.int/pdfs/human/ich/053900en.pdf

Section 2.2 (page 2)

Point 3 "*Ligand binding or enzyme assay data suggesting a potential for adverse effects*" should be modified as follows: "*Data from assays of receptors, enzymes, transporters or ion channels activity suggesting a potential for adverse events*".

Section 2.7.2 (page 5) - Core battery - Cardiovascular system

Recommend to change the 2nd sentence from: "*In vivo, in vitro and/or ex vivo evaluations, including methods for repolarization and conductance abnormalities, should also be considered.*" to "*In vivo, in vitro and/or ex vivo evaluations, including methods for repolarization and conductance abnormalities should also be carefully considered.*"

Consequently the "Note 3" reference and the Note 3 itself (**Section 3.3 - Page 8**) should be deleted.

Section 2.7.3 (page 5) - Core battery - Respiratory system

Recommend changing the current section from " *Effects of the test substance on respiratory function should be assessed appropriately. Respiratory rate and other measures of respiratory function (e.g., tidal volume (6) or hemoglobin oxygen saturation) should be evaluated. Clinical observation of animals is generally not adequate to assess respiratory function, and thus these parameters should be quantified by using appropriate methodologies."* to *"Effects of the test substance on respiratory function should be assessed appropriately and should include measures of both ventilatory and airway functions. Respiratory rate, tidal volume and derived minute volume (total pulmonary ventilation) should be quantified to evaluate ventilatory function, while airway resistance or conductance should be quantified to evaluate airway function."*

Section 2.8.1.2 (page 6) - Follow-up studies - Cardiovascular system

Recommend adding the text, *"Additional studies to further evaluate effects on cardiac electrophysiology."* We should keep this broad, since the in vivo ECG data may indicate a PR effect and we'd want to follow-up with a sodium channel study, for example. In other words, we should not just think about repolarization.

Section 2.8.1.2 (page 6) - Follow-up studies - Respiratory system

Recommend changing the current section from "*Airway resistance, compliance, pulmonary arterial pressure, blood gases, blood pH, etc.*" to *"Arterial blood gases and pH, lung compliance, lung capacities and forced expiratory flows, ventilatory responses to central and peripheral chemoreceptor stimulants, effect of vagotomy on ventilatory response, phrenic nerve activity and/or respiratory muscle function, inhaled carbon monoxide diffusion capacity, airway responses to inhaled bronchoconstrictors (airway reactivity), pulmonary artery and wedge pressures".*